REMARKS

Applicants thank the Examiner for indicating that claims 26 and 27 are free of the prior art and are allowable.

Claims 1-4, 7, 8, 10-13 and 25-27 were pending in the application. New claims 28 and 29 have been added. Accordingly, claims 1-4, 7, 8, 10-13 and 25-29 are currently pending in the application.

Support for new claims 28 and 29 can be found throughout the specification and the claims as originally filed, for example, at least at page 2, lines 7-25; page 9, line 19 through page 10, line 8; page 10, lines 16-26; page 13, lines 9-20

No new matter has been added. Any amendment and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was performed solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 1-4, 7, 8, 10-13 and 25 Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of claims 1-4, 7-8, 10-13 and 25 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner states that

> [t]he specification does not describe a regulatory element of any size in any other non-human animal that can direct testis or ovary specific gene transcription. The specification also fails to describe any fragments larger than 300 bp isolated from either 5' or 3' of the mouse GDF-9 gene that can direct ovary or testis specific transcription.

Moreover, the Examiner is of the opinion that the

> specification fails to teach what is the critical/essential element that the claimed polynucleotide must have for its function of regulating expression in oocyte or testis...Since the specification does not describe what are necessary elements within the 3.2 and 10kb fragments for the claimed regulating function in oocytes

> or testis, the correlation between the minimal structure and the function has not been established...without the correlation of the function of the claimed sequence and the minimal structure (the sequence, in the instant case), one of skilled in the art would not know how to envision the structure of the claimed genus of polynucleotides.

Applicants respectfully traverse the foregoing rejection for the reasons previously made of record, the substance of which is reiterated herein. The pending claims are drawn to isolated polynucleotides having specific structural and functional characteristics. Specifically, the claimed polynucleotides are capable of regulating expression of an operably linked gene in oocytes or testis. Further, the claimed polynucleotides include the first 10 kilobases of DNA of the murine GDF-9 gene immediately 5' of the transcription start site or DNA at least 95% identical thereto, the first 3.3 kilobases of DNA of the murine GDF-9 gene immediately 5' of the transcription start site or DNA at least 95% identical thereto, the first 1 kilobase of DNA of the murine GDF-9 gene immediately 3' of the transcription termination site. The claims are also drawn to portions of the foregoing polynucleotides wherein the portion is at least 300 nucleotides in length. Based on Applicants' teachings (described below) and the level of skill in the art, one of ordinary skill would have recognized that Applicants were in possession of the claimed invention.

An objective standard for determining compliance with the written description requirement under 35 U.S.C. § 112, first paragraph, is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicants were in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) and *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Furthermore, pursuant to MPEP § 2163(II)(D) "[f]actors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406."

Indeed, it is firmly established that the descriptive text needed to meet the Written Description requirement varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). In *Capon*, the Federal Circuit explained that "since the law is applied to each invention in view of the state of the relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science." *Id.* Specifically, the Court stated that:

> Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter ***depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter***. *Id.* at 1359 (emphasis added).

For example, Applicants' disclosure provides methods for identifying the claimed GDF-9 regulatory elements, including those with a nucleotide sequence at least 95% identical to murine GDF-9[1] (see, *e.g.*, page 11, line 26 through page 13, line 20) of the instant specification. Moreover, Applicants disclose assays to test whether these variants are capable of regulating expression of an operably linked gene in oocytes or testis (see page 16, lines 5-18 of the instant specification). Applicants' disclosure also provides a detailed description of how to identify and characterize the claimed GDF-9 molecules from variety of sources including mammalian and avian genomic cDNA libraries or synthesized from a variety of known and sequenced GDF-9 genes (see, *e.g.*, page 9, line 19 through page 13, line 29). Applicants further teach methods for preparing expression vectors which comprise the identified regulatory elements, as well as methods for transfecting cells with such vectors (see, *e.g.*, page 14, line 1 through page 16, line 29). Further, the specification provides working examples which demonstrate how to the claimed molecules can be tested for regulating expression of genes as claimed (see, *e.g.*, page 19, line 6 through page 22, line 4). Moreover, as indicated by the Guidelines, "procedures for making variants...which have 95% identity...and retain its activity are conventional in the art."

With regard to the claimed polynucleotide portions which are at least 300 nucleotides in length, Applicants teach in the present specification that the sizes of the regulatory elements are variable (see, *e.g.*, page 7, lines 4-5). Applicants further identify (at page 11, lines 3-25) the

presence of a testis-specific repressor element in the region from 3.3 to 10 kilobases immediately 5' of the transcription initiation site of the mouse GDf-9 gene. Accordingly, based on the level of skill in the art at the time the present application was filed, Applicants teach that "[f]urther mapping of such promoter and repressor elements can be achieved by similarly testing smaller fragments of these regions to define the particular sequences involved in gene regulation." Applicants also teach that other functional mapping techniques also may be employed to further characterize and identify specific GDF-9 regulatory sequences.

> For example, nucleotide bases within these regions (e.g., the 0.3, 3.3 or 10 kilobase fragments of the 5' region) can be mutated by, for example site-directed mutagenesis, to add, delete or change one or more bases (e.g., 6-12 bases), followed by testing the mutated regulatory sequences for activity either *in vitro* (e.g., by microinjection or transfection) or *in vivo* (e.g., in a transgenic animal) to see what functional effect the mutation had. From this information, nucleotide bases required for function (e.g., upregulation or downregulation) of the regulatory element can be determined. For example, if upon mutating a small (e.g., 6-12 base pair) segment of the 5' region of a GDF-9 gene, transcription levels of a reporter gene operatively linked to the 5' region are diminished, then this small region can be concluded to be involved in promoting transcription (e.g., by binding to one or more transcription factors). Transcription factors that bind cis-acting regulatory elements may also interact with each other. Therefore, multiple reporter constructs can be developed and tested for the interaction between their potential cis-elements and such binding proteins using the assays described herein.

Alternatively, according to Applicants, "regulatory regions of GDF-9 genes can be identified by comparing untranscribed upstream and downstream regions, and transcribed, untranslated regions of a GDF-9 gene with 5' and 3' sequences from other known genes, for example, which are expressed is a similar tissue-specific pattern and, therefore, which may contain related or homologous regulatory elements." (see, *e.g.*, page 12, lines 14-27). Applicants further exemplify a polynucleotide which is 300 nucleotide in length and which contains a conserved domain that has been shown to bind basic helix-loop-helix transcription factors, many of which are tissue-specific (Liang et al. (1997) *Development* 124:4939-4947).

Thus, based on the extensive teachings in Applicants' specification regarding the structural and functional properties of the claimed regulatory elements, as well as the knowledge generally available in the art, the skilled artisan would understand that Applicants were in

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[1] Applicants draw the Examiner's attention to Example 14 of the Revised Interim Written Description Guidelines, Training Material (published in the Federal Register on December 21, 1999).

possession of the claimed invention at the time of filing. Accordingly, the requirement of 35 U.S.C. § 112, First Paragraph for written description has been satisfied and Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney could be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

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Respectfully submitted,

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